REVIEW ARTICLE

Respiratory Infections Caused by Environmental Mycobacteria

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Introduction

The subject of this review article is complex for the following reasons: there is no general agreement on a name for this group of mycobacteria; new species that are pathogenic to differing degrees are constantly being described; even when the potential pathogenic capacity of a given species is known, whether the organism in question is the cause of the patient's illness must be determined on a case-by-case basis; diagnosis is difficult; and there is uncertainty concerning what drugs should be used and the optimum duration of treatment. Our aim is to provide an up-to-date review of these topics bearing in mind that excellent general reviews of the literature reflecting the views of various scientific associations have recently been published in Spain and elsewhere.[1-4]

This group of mycobacteria produce pulmonary, nodal, and disseminated disease, although disease may affect other sites, such as the soft tissues, bone, and the genitourinary apparatus.[1] This review deals exclusively with the respiratory infections.

Terminology and Definition

Various general names have been used to refer to the mycobacteria that do not belong to the *Mycobacterium tuberculosis* and *Mycobacterium leprae* groups[5]: atypical mycobacteria (to differentiate them from the more common *M tuberculosis*, although this label does not adequately differentiate them from the nontuberculous *M leprae* group); nontuberculous mycobacteria[1] (even though they produce lesions with tubercles); mycobacteria other than tuberculosis or MOTT, a long-winded term difficult to render in Spanish; opportunist mycobacteria[2] (an inappropriate term since it includes microorganisms that have never demonstrated any pathogenic potential in humans); and environmental mycobacteria (because they are found widely distributed throughout the environment, although some strains have recently been found in human specimens and not in the environment).[6] Environmental mycobacteria is not a term commonly used in the English-language literature. There is no consensus on the use of any one term, and at present authors and scientific bodies use whatever term they prefer. The Working Group on Tuberculosis and Respiratory Infections (TIR) of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) is in favor of *a)* a systematic and preferential binomial denomination (genus and species), and *b)* using the term environmental mycobacteria (EM) to denote the group as a whole.[3]

Epidemiology and Pathogenesis

EM are found in the environment: water (including tap water), soil, dust, milk, foodstuffs, birds, and other animals.[1] Since they can inhabit the surfaces and secretions of the body without causing illness, until the second half of the last century their presence was considered to represent contamination or colonization. With improved diagnostic techniques and the description of their clinical presentation, the importance of these EM has increased. Another factor has been their observed predisposition to infect patients with immunodeficiency, especially that caused by the human immunodeficiency virus (HIV).[7]

The mechanism by which the disease develops is poorly understood; infection gives rise to granulomatous lesions indistinguishable from those produced by *M tuberculosis*, so it is thought that the pathology is similar. Lung infection caused by EM is probably acquired by inhalation of aerosolized natural water or water from domestic or institutional water systems; another point of entry is the digestive system, leading to disseminated infection, including lung infection. It is not known how often the disease is caused by reactivation and how often by exogenous reinfection. Although there is a high prevalence of skin test reactivity to *M avium*, disease caused by this mycobacterium is rare. It is thought, therefore, that the immune system effectively contains and eliminates the infecting microorganisms. Lung disease caused by EM occurs in patients with prior lung disease of other types or deficient immune systems, although it is also found in individuals with no prior disease. Studies using DNA techniques, serology, and

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skin tests have shown that these mycobacteria are not very contagious even when patients are smear positive. This finding has practical implications. If EM are found in a patient who has been erroneously diagnosed with tuberculosis, the contact investigation and any treatment for latent tuberculosis infection that may have been initiated should be suspended.[8]

Although Runyon's classification of mycobacteria based on phenotypic characteristics (growth and pigmentation) (Table 1) is somewhat dated (1959) and does not therefore include more recently discovered organisms, it is, nonetheless, useful in classifying the most important species from a clinical point of view. Moreover, it has been observed that there is a high degree of correlation between genotypic and phenotypic characteristics in most of the newly discovered species, giving rise to phylogenetic trees that group the different mycobacteria.[6]

The number of species is very large and is growing as the means used to identify them improve,[6-9] but only a limited number of species are pathogenic, with incidence varying by geographic region. The chief pathogens that cause lung disease are *M kansasii, M malmoense, M xenopi, M avium* complex, *M fortuitum, M abscessus, M celatum, M asiaticum,* and *M szulgai*. *M gordonae* is an EM frequently detected as a contaminant but only rarely as a true pathogen.[10] Recently described EM have varying pathogenic potential and are generally rare. A detailed description of these species is beyond the scope of this review.[6-9] Spanish authors have isolated and described 4 new EM species: *M gadium,*[11] *M alvei,*[12] *M brumae,*[13] and *M mageritense.*[14]

A list has been compiled of all the EM isolated in Spanish clinical microbiology laboratories (1 species per patient) between 1976 and 1996. The number of isolates increased gradually over this period, with a sharp increase in 1991. Of all the EM isolates found in 26 laboratories, 56.96% correspond to the final 4 years of the study (1993-1996). The 6 most common species were *M gordonae* (20.5%), *M xenopi* (19.4%), *M avium* complex (19.1%), *M fortuitum* (10.5%), *M kansasii* (6%), and *M chelonae* (5.5%).[15] In a Spanish study of 88 patients diagnosed with disease caused by EM between 1989 and 1997, *M kansasii* was the most prevalent EM (54%), followed by *M avium* complex (40%). In HIV infected patients, however, *M avium* complex was predominant (61%), while in non-HIV patients the predominant EM was *M kansasii* (76%).[16] In Spain, as in the United Kingdom,[17] the distribution of EM varies by geographical region.[15]

TABLE 1
Classification of Mycobacteria That Often Cause Infections in Humans (Runyon, 1959)*

M tuberculosis complex
M tuberculosis
M bovis
M africanum
M leprae
Slow growing mycobacteria (more than 7 days)
M kansasii (photochromogens, Runyon Group I)
M marinum
M gordonae (scotochromogens, Runyon Group II)
M scrofulaceum
M avium complex (nonchromogens, Runyon Group III)
M avium
M intracellulare
M scrofulaceum
M terrae complex
M ulcerans
M xenopi
Rapidly growing mycobacteria (Runyon Group IV)
M fortuitum
M chelonae
M abscessus

**M* indicates *Mycobacterium.*
Runyon EH. Anonymous mycobacteria in pulmonary disease. Med Clin North Am. 1959;43:273-90. Taken from Griffith y Wallace.[7]

Bacteriologic Diagnosis

The role of the microbiological laboratory in the diagnosis of respiratory infections caused by EM comprises the detection, isolation, and identification of the mycobacteria as well as subsequent measurement of their susceptibility to antimycobacterial drugs. Respiratory specimens are handled in the usual way: digestion and decontamination, concentration using a centrifuge, microscopic examination of the concentrated samples once they have been stained using the method best suited to the laboratory in question, and inoculation of the culture media. The most widely used staining methods are fluorescent auramine-rhodamine dyes, Ziehl-Neelsen, and Kinyoun (under the microscope the EM are indistinguishable from other mycobacteria). The samples should be inoculated simultaneously onto a solid medium (Löwenstein-Jensen, Coletsos or Middlebrook 7H10 or 7H11, or similar) and into a liquid medium, preferably one with an automated reading system (BACTEC 460, BacTAlert 3D, MGIT, MB9000, ESP, etc). The use of automated liquid culture systems improves diagnostic yield up to 25%,[18] detects the growth of mycobacteria more quickly, obviates unnecessary handling, and facilitates more rapid identification of the mycobacteria when used in conjunction with molecular biology techniques.

The different species of mycobacteria can be identified using:

1. Conventional phenotypic methods[6,19]: pigmentation pattern, growth characteristics, and biochemical tests. These methods are complex and extremely slow (taking 4 to 8 weeks), and their ability to discriminate is very limited since any phenotypic pattern can be common to more than a single species. This was the method of choice until a little over 10 years ago. Alternative methods are based on the analysis of lipid profiles and/or mycolic acids using various chromatographic techniques. Although such methods are more precise, their use is limited to a few top level laboratories because they are costly and complex.

2. Genotypic methods[6,19]: various molecular biology techniques that use stable and well conserved nucleic acid sequences found in the genus *Mycobacterium* as a target. The most commonly studied genes are *hsp65* kd and the *16S* ribosomal RNA gene. These techniques are very precise and much faster, and it is possible to work directly with both liquid and solid primary cultures. The following are the principal molecular techniques: nucleic acid probes that identify *M tuberculosis* complex, *M kansasii, M avium* complex, and *M gordonae* in under 1 hour; reverse hybridization,[20] which makes it possible to identify up to 16 mycobacterial species in just a single step within 5 hours and to identify mixed cultures; the so called PRA technique[21] (polymerase chain reaction with restriction enzyme pattern analysis), which increases the number of species that can be identified in a single step and in just a few hours to 34; and *16S* ribosomal RNA gene sequencing,[22,23] which is currently considered to be the best method of identifying mycobacteria. It is not necessary to sequence the complete gene since the information contained at the 5' end is sufficient to specifically identify most species of mycobacteria within 12 to 36 hours. When difficulties are encountered in the identification of an EM, helpful resources are available on the Internet.[24,25]

Clinical Picture and Radiography

M kansasii

Unlike other EM, *M kansasii* is found in tap water rather than in natural soil or water, and consequently *M kansasii* –related disease occurs in areas where drinking water is found, most often in urban areas.[26,27] The clinical and radiographic presentation when infection affects the lungs (the site most often affected by *M kansasii*[26]) is similar to that of tuberculosis, and it is the EM-related disease that most resembles tuberculosis[26,28] with cavitation occurring in a high percentage of cases (76%).[27] There are, however, radiographic differences between the two: mainly, the presence of pleural effusion makes it unlikely that the disease is caused by *M kansasii.*[29] Infection with *M kansasii* is more common in males,[27,30] and the most common predisposing factors are chronic obstructive pulmonary disease (COPD), a history of tuberculosis, smoking, alcoholism, pneumoconiosis, and HIV infection.[26] The likelihood of infection by *M kansasii* increases when pneumoconiosis and HIV infection are associated.[31,32] A higher incidence has also been found in people in poor socioeconomic situations.[17,30] In 40% of cases, the disease has been diagnosed in immunocompetent individuals with no predisposing risk factors.[17,30]

M avium *complex*

M avium complex includes 2 species, *M avium* and *M intracellulare*, which both cause lung disease with variable and non-specific symptoms. The 3 basic clinical signs of such disease are *a)* fibrocavitary disease clinically and radiographically similar to tuberculosis and predominantly affecting middle-aged or older male smokers with chronic obstructive pulmonary disease,[33] although this clinical presentation may also occur in individuals without predisposing factors; *b)* development of disease in areas of bronchiectasis, which can occur in patients with prior tuberculosis who present new radiographic infiltrates, or in patients with cystic fibrosis[33]; and *c)* the presence of bronchiectasis and nodules, a clinical picture that appears in immunocompetent, nonsmoking women over 50 with no history of lung disease, with cough and small nodules in the chest radiograph that become progressively larger,[34] or with bronchiectasis and nodules.[35] When it presents in this form, the disease can be difficult to diagnose and develops progressively, making prompt initiation of treatment essential.[34,36] In this context, computed tomography (CT) will reveal the presence or absence of pulmonary hyperinflation, and pulmonary nodules or bronchiectasis predominantly affecting the middle lobe or the lingula.[37,38] However, other clinical presentations have also been reported. In 1 case series, a higher incidence of scoliosis and *pectus excavatum* was found in *M avium* complex infected patients than in the general population or patients with tuberculosis.[39] Another clinical form of the disease is Lady Windermere syndrome, which affects women of advanced age with abnormalities (bronchiectasias or nodules) affecting the lingula or the middle lobe.[40] Finally, illness caused by *M avium* complex may present as hypersensitivity pneumonitis or extrinsic allergic alveolitis in a condition called hot tub lung, which is related to bathtub water. In some cases, this disease improved with corticosteroids and in others with antibiotics, making it unclear whether the pathogen is infectious, immunological, or both.[41,42]

Rapidly Growing Mycobacteria

Rapidly growing mycobacteria are environmental saprophytes widely distributed in nature and capable of resisting environments affected by extremely harsh temperature and nutritional conditions. They have been isolated in soil, dust, water, land and aquatic animals, hospital environments, and contaminated reagents.[7] Of particular interest are three non-pigmented species: *M fortuitum, M abscessus,* and *M chelonae.* The first 2 are the species that most often cause lung disease *(M abscessus,* 82%; *M fortuitum,* 13%). Non-smokers (66%) and women (65%) predominate among patients with these infections, and the mean age is 58 years. A long period elapses between the initial symptoms (cough) and diagnosis. The radiographic signs of the disease are interstitial, interstitial-alveolar, or reticulonodular infiltrates in the upper lobes (88%), with bilateral involvement in 77% of cases, and cavitation in 16%. Predisposing factors include prior mycobacterial infection (mainly tuberculosis), concurrent infection by *M avium*, cystic fibrosis, and

gastrointestinal diseases that cause vomiting. No predisposing factor is found in 32% of cases.[43] Bronchiectasis and nodules similar to those described in cases of infection with *M avium*[44] may appear on CT scans. These are also similar to the signs described for lung disease caused by *M chelonae.*[45] As with other EM diseases, atypical signs may appear, such as the presence of a single pulmonary nodule, similar to a case described by a Spanish author.[46]

Mycobacterium terrae

Discovered in 1950, *M terrae* is included in *M terrae* complex along with *Mycobacterium triviale* and *Mycobacterium nonchromogenicum* (Runyon's group III). While not initially considered to be a pathogen, it has been observed to cause illness, mainly in joints (tenosynovitis). Lung disease is found in 26% of cases (14 patients out of a total of 54 cases described in a recent review,[47] and 1 further case reported in Spain[48]). Pulmonary infection with *M terrae* can result in a cavitary process with noncaseating granulomas in tissue samples. No predisposing factors are found in 44% of patients with disease caused by *M terrae* complex.

M xenopi

Discovered in 1959, *M xenopi* is isolated in hot water and is a frequent contaminant in laboratories. It has also been isolated in bronchoscopes. Cases of lung disease caused by this pathogen have been reported, and it can cause nosocomial infections. The disease particularly affects male patients with COPD (75%) and it gives rise to radiographic abnormalities, especially nodules or masses, as well as cavitary lesions in the upper lobes that can be indistinguishable from those caused by tuberculosis.[9,49,50] In recent years, the number of isolates of this mycobacteria has increased owing to the improvement in culture media.[51] Since it may be a pathogen as well as a contaminant, its isolation should be interpreted in an appropriate clinical context because it may cause disease which, particularly in patients with acquired immunodeficiency syndrome (AIDS), can be severe and progressive.[52-54]

M malmoense

First described in Sweden in 1977, *M malmoense* causes lung disease. Most reported cases have been in the United Kingdom and Scandinavia,[55-57] while infection with this mycobacterium is less common in the United States of America.[58,59] In a recent case series, 56% of patients had predisposing pulmonary factors (emphysema, asthma, healed tuberculosis), and cavitation was observed on the radiographs of 74%, with unilateral involvement in 52%.[55] The abnormalities observed on the chest radiographs of patients with this disease are indistinguishable from those caused by tuberculosis.[60]

EM and AIDS

Disease caused by *M avium* complex was one of the first opportunistic infections described in the early years of AIDS. It basically took the form of a disseminated infection (with lung involvement in 5%-15% of cases) that correlated with the patient's CD4+ lymphocyte count (in general a count of <50 cells/µL is associated with the appearance of disseminated disease). The disease is also related to a plasma concentration greater than 100 000 copies/mL of HIV RNA.[61,62] The same pattern occurs with the other EM: the greater the immune deficiency, the higher the frequency of disseminated disease (approximately 20% of disseminated disease in this setting is caused by *M kansasii).*[62] It should, therefore, be borne in mind that the more severe the patient's immune deficiency, the more likely it is that the presence of an EM will be clinically significant and require treatment.[52]

The incidence of disease caused by EM and the proportion of disseminated disease both decrease greatly after patients start antiretroviral therapy, an effect related to the increase in CD4+ cell counts produced by such treatment.[63]

Another aspect of retroviral therapy is the possible appearance of "immune reconstitution syndrome" when an EM infection manifests itself after the immune response has recovered as a result of antiretroviral treatment (this syndrome has also been described in cases of infection with *M tuberculosis*, cytomegalovirus, and hepatitis B and C virus). This phenomenon has been interpreted as an immune reaction to a specific pathogen in response to an infection previously present but clinically undetected. The clinical features are generally mild (fever and lymphadenopathy, which appears wherever the infection was latent), and in most cases they disappear when antiretroviral treatment is continued. In some cases it may be necessary to administer corticosteroids. Disease usually appears a few weeks after initiation of retroviral treatment, although it can occur as much as a year later.[62]

Mycobacteria and Cystic Fibrosis

Cystic fibrosis is cited as a risk factor for the development of EM diseases, although the prevalence of EM in the sputum of cystic fibrosis patients varies from one case series to another (from 4% to 19%).[64] A recent prospective study reported that 13% of patients with cystic fibrosis who were 10 years or older had EM in sputum; in most cases the isolate was *M avium* complex (72%) and *M abscessus* (16%). The authors used molecular studies to show that neither patient-to-patient transmission nor nosocomial acquisition explained the high prevalence of EM. Some 20% of patients with a positive culture of some kind (3% of all cases studied) satisfied the criteria for disease defined by the American Thoracic Society (ATS). Over 25% of patients in whom

some type of EM was isolated had 1 positive sputum smear, and in 13% all 3 sputum cultures were positive. The authors of the study did not draw any conclusions regarding the clinical significance of these findings, but advanced the hypothesis that these patients present a mild form of disease that might progress over time, since the group of patients who had EM in sputum was older than the group who did not.[65] For all of the above reasons, diagnosis of EM-related disease in patients with cystic fibrosis is difficult. Consequently, when the clinical picture (symptoms, lung function, radiographic signs) continues to deteriorate in a patient with positive cultures despite appropriate conventional treatment of their underlying disease, the advisability of initiating treatment for disease caused by EM should be considered. Conversely, if no symptoms of disease are found and the patient's condition is stable, clinical follow up may be the best course of action.[64]

TABLE 2
Diagnosis of Pulmonary Disease Caused by Environmental Mycobacteria*

1. Clinical criteria
- *a)* Compatible signs and symptoms (the most common are cough and fatigue; fever, weight loss, hemoptysis, and dyspnea may be present, particularly in advanced disease) with deterioration in clinical status if an underlying condition is present
- *b)* Exclusion of other disease that would explain condition, or adequate treatment of the other disease accompanied by an increase in signs and symptoms

2. Radiographic criteria
- *a)* Any of the following abnormalities (with evidence of progression if abnormalities have been present for more than 1 year):
  Infiltrates with or without nodules
  Cavitation
  Multiple nodules
- *b)* Any of the following HRCT abnormalities:
  Multiple small nodules
  Multifocal bronchiectasis with or without small lung nodules

3. Bacteriologic criteria
- *a)* At least 3 available sputum/bronchial wash samples within 1 year
  3 positive cultures with negative AFB smears
  2 positive cultures and 1 positive AFB smear
- *b)* Single available bronchial wash and inability to obtain sputum samples
  Positive culture with 2+, 3+, or 4+ growth (1+ growth is sufficient in patients with severe immunodeficiency). The same in HIV-infected patients with CD4+ <200 and excluding M avium complex
  Positive culture with a 2+, 3+, or 4+ in AFB smear (0 to 4+ depending on the degree of growth on culture or the number of bacilli in AFB smear)
- *c)* Tissue biopsy
  Any growth from bronchopulmonary tissue biopsy
  Granuloma and/or positive AFB on lung biopsy with 1 or more positive cultures from sputum/bronchial wash
  Any growth from usually sterile extrapulmonary site

For a diagnosis all 3 criteria must be satisfied (clinical, radiographic, and bacteriologic)

*HRCT indicates high resolution computed tomography; AFB, acid fast bacilli; HIV, human immunodeficiency virus. Taken from the American Thoracic Society.[1]

Diagnosis

Pulmonary disease caused by EM is the result of infection with different species of mycobacteria, which are more or less virulent and give rise to different clinical presentations. The resulting clinical picture is also affected by the host's susceptibility to infection.[66] When there is an underlying lung disease, it can be difficult to determine whether symptoms are attributable to this or to the EM infection. All of these circumstances make it difficult to define universally applicable diagnostic guidelines, although the ATS has published widely accepted guidelines (Table 2).[1] These recommendations are based on experience with the most common forms of EM (*M avium* complex, *M kansasii,* and *M abscessus)* and, although this has not been demonstrated, it is assumed that they are equally valid for the other EM.[66] It is difficult to apply the ATS guidelines when an EM is isolated in a single sputum sample because there is no guideline for interpreting a single positive sputum culture. This problem cropped up in a recent study on lung disease caused by *M kansasii* in HIV seropositive and seronegative South African miners in which only 27% of patients fulfilled the ATS criteria because the remainder had only 1 positive sputum culture. Treatment was initiated in patients with a single sputum isolate of *M kansasii* if diagnosis was supported by corroborating clinical and radiographic features.[31] This does not mean that treatment should be initiated in patients with a single isolate in the absence of clinical or radiographic signs consistent with the diagnosis. Problematic cases should be managed on the basis of the sound clinical judgment of a physician with experience treating these diseases, consultation with experts, or by periodic monitoring.[66]

Another problem is the use of the term "colonization" to describe the situation when EM is isolated in the secretions of patients with no apparent lung disease.[67] This term should be avoided, particularly in patients with *M avium* because unusual presentations have been found in these patients. These have been discussed in the section on clinical features (in fact granulomatous lesions have been found in the bronchiectasis of patients with *M avium).*[68] For all of these reasons, patients with cultures positive for *M avium* should be monitored for lung abnormalities, in particular bronchiectasis in CT scans. Likewise, in patients with idiopathic bronchiectasis, samples should be cultured to rule out disease caused by *M avium.*[69] In short, the isolation of EM in cultures obliges us to exclude the possibility that an underlying disease really exists, whereas when positive cultures are found in patients without apparent disease, a periodic checkup may be the preferred option.

We may conclude that the clinical significance of an isolate in human secretions or tissue depends on the type of specimen in which the organism is isolated, the number of isolates, the degree of growth, and the identity of the mycobacteria found. All of the above are

TABLE 3
Treatment of Disease Caused by Environmental Mycobacteria*

Mycobacterial Species	Clinical Presentation	First Line Treatment	Alternative Treatment
M kansasii	Pulmonary	Rifampicin (or rifabutin) + ethambutol + isoniazid	Clarithromycin Sulfamethoxazole Streptomycin Amikacin
	Disseminated	Rifampicin (or rifabutin) + ethambutol + isoniazid	Clarithromycin Sulfamethoxazole Streptomycin Amikacin
M avium complex	Pulmonary	Clarithromycin or azithromycin + rifabutin or rifampicin + ethambutol ± an aminoglycoside in the early stages	Isoniazid Streptomycin Amikacin Fluoroquinolones Clofazimine Ethionamide
	Disseminated	Clarithromycin or azithromycin + rifabutin or rifampicin + ethambutol ± an aminoglycoside in the early stages	Streptomycin Amikacin Fluoroquinolones Clofazimine
M xenopi	Pulmonary	Macrolide + rifabutin or rifampicin + ethambutol ± an aminoglycoside in the early stages	Fluoroquinolones
M malmoense	Pulmonary	Rifampicin + ethambutol + a macrolide or fluoroquinolone?	
M simiae	Pulmonary	Clarithromycin + ethambutol + rifampicin + streptomycin	
M szulgai	Pulmonary	Clarithromycin + ethambutol + rifampicin + streptomycin	
M terrae	Pulmonary	Clarithromycin + ethambutol + rifampicin	
M asiaticum	Pulmonary	Rifampicin + ethambutol + an aminoglycoside + isoniazid or pyrazinamide	
M fortuitum	Pulmonary	Choose 2 drugs to which it is susceptible depending on results of susceptibility testing (fluoroquinolones, macrolides sulfonamide, doxycycline, minocycline)	Amikacin Cefoxitin Imipenem
M abscessus, *M chelonae*	Pulmonary	Depending on susceptibility tests, clarithromycin + 1 or 2 parenteral drugs (amikacin/tobramycin, cefoxitin, imipenem)	Fluoroquinolones Doxycycline

*M indicates *Mycobacterium.*

also influenced by the clinical presentation since the presence of preexisting abnormalities favors the development of disease in immunocompromised patients and patients with lung infections.

Treatment

Once a diagnosis of EM pulmonary disease has been established according to the criteria set out above, treatment will depend mainly on the species of mycobacteria isolated, the extent of the disease, and the patient's immune status. Although some medical associations have published guidelines—the ATS,[1] the British Thoracic Society (BTS),[2] and SEPAR[70]—no consensus has been reached on the optimal treatment of EM infections because of the lack of randomized controlled trials, the limitations of in vitro testing of antituberculosis drugs, and the discrepancies between susceptibility test results; while resistance is often found to such drugs in vitro, a good clinical response is obtained when they are used to treat patients with EM infections.[71-74] The use of appropriate therapy as defined by the ATS and BTS guidelines has been associated with a higher success rate (74%) than that achieved before these recommendations were published (24%).[17] A summary of the most widely accepted treatments for disease caused by EM is shown in Table 3.

Guidelines on antimicrobial susceptibility testing have been published. These address the limitations of such tests and the difficulties associated with their interpretation.[1,4] Recommendations vary by the group or species of EM being tested. Systematic susceptibility testing is not recommended in all cases of EM infection, but it may be advisable in certain circumstances, for example to provide baseline data that will be useful if the patient does not respond to treatment or suffers a relapse. In the case of *M avium* complex, when and how susceptibility testing should be performed remains controversial.[71] Since most strains of *M avium* complex are resistant to the low drug concentrations of isoniazid, rifampicin, ethambutol, and streptomycin used for testing the susceptibility of *M tuberculosis*, susceptibility testing of *M avium* complex isolates to antituberculosis drugs is not recommended. Other drugs have also been tested, including macrolides, quinolones, rifabutin, amikacin, and clofazimine, but the use of susceptibility tests before initial treatment is not recommended because of the difficulty of interpreting

TABLE 4
Antiretroviral Agents and Rifamycins Recommendations and Dose Adjustments

Protease Inhibitors	Rifabutin	Rifampicin
Indinavir	↓ dose to 150 mg/day or 300 mg 3 times a week	Contraindicated
Nelfinavir	↓ dose to 150 mg/day or 300 mg 3 times a week	Not recommended
Amprenavir and fosamprenavir	↓ dose to 150 mg/day or 300 mg 3 times a week if CD4+ <100/µL	Not recommended
Atazanavir	↓ dose to 150 mg/day or 150 mg 3 times a week if CD4+ <100/µL	Not recommended
Lopinavir	↓ dose to 150 mg/day or 150 mg 3 times a week	Not recommended
Ritonavir	↓ dose to 150 mg/day or 150 mg 3 times a week	Not recommended if ritonavir is the only protease inhibitor
Saquinavir	Contraindicated except if ritonavir/saquinavir ↓ dose to 150 mg/day or 150 mg 3 times a week if CD4+ <100/µL	Contraindicated except if ritonavir/saquinavir: 400/400 mg mg twice daily R 600 mg/day or 3 times a week
NNRTI	**Rifabutin**	**Rifampicin**
Nevirapine	Dose need not be adjusted	Not recommended but should be monitored if used
Delavirdine	Not recommended	Contraindicated
Efavirenz	↑ dose to 450-600 mg/day or 600 mg 3 times a week	Dose need not be adjusted Consider ↑ efavirenz to 800 mg/day

*NNRTI indicates nonnucleoside reverse transcriptase inhibitors; R, rifampicin.

the results. The only indication for susceptibility testing against macrolides would be in samples from patients who have received prophylaxis or prior treatment with these drugs.[75] Although *M kansasii* is initially susceptible to rifampicin, acquired resistance may develop, so testing for susceptibility to rifampicin is recommended at the beginning of treatment and in the case of treatment failure or relapse. Any rifampicin-resistant strains found should be tested for susceptibility to the new macrolides, quinolones, aminoglycosides, and sulfonamides.[76,77] In the case of other slow growing mycobacteria, susceptibility tests may provide useful information, and such strains should also be tested against macrolides, quinolones, rifampicin, aminoglycosides, isoniazid, and sulfonamides.[1,4] Susceptibility testing of rapidly growing mycobacteria is recommended for all clinically significant isolates, and in the case of treatment failure or relapse. These tests should not be performed with first line antituberculosis drugs. Other antibacterial agents are used in such cases, including amikacin, fluoroquinolones, macrolides, doxycycline, cefoxitin, imipenem, and sulfonamides.

Treatment of M kansasii *Infection*

Rifampicin is the first line therapy for *M kansasii* infection because its use has significantly increased the efficacy and shortened the duration of treatment, raising 4-month sputum conversion rates to almost 100% and reducing treatment failure and relapse to about 1%.[78,79] Untreated wild strains of *M kansasii* are usually susceptible in vitro to rifampicin, rifabutin, isoniazid, ethambutol, ethionamide, amikacin, streptomycin, clarithromycin, fluoroquinolones, and sulfamethoxazole at concentrations easily achieved in serum with therapeutic doses[27,76-78,80]; they are generally resistant to pyrazinamide, capreomycin, and p-aminosalicylic acid. There are currently differences of opinion concerning treatment in the official guidelines published by the medical associations: the ATS recommends treatment with rifampicin (600 mg), isoniazid (300 mg), and ethambutol (25 mg/kg for the first 2 months followed by 15 mg/kg) given daily for 18 months with at least 12 months of negative sputum cultures[1]; the BTS recommends treatment with rifampicin (600 mg or 450 mg for patients weighing under 50 kg) and ethambutol (15 mg/kg) given daily for 9 months in immunocompetent patients, but prolonged for 15 to 24 months or until sputum has been negative for 12 months in immunocompromised patients[2]; SEPAR, on the other hand, recommends 12 months of treatment with rifampicin, isoniazid, and ethambutol.[70] Other authors have reported the results of short course treatments lasting between 9 and 12 months. Such treatments yield similar results in terms of conversion to negative sputum culture but are associated with a higher percentage of relapses, between 2.5% and 15.3%,[27,79,81-83] than the more prolonged treatments. Many experts consider that it is important to continue treatment for at least 12 months after conversion to culture negative.[26] If patients are intolerant to any of these drugs, clarithromycin is the recommended alternative treatment because of its good in vitro activity against *M kansasii* and its excellent in vivo activity against other EM.[4,22,84] Patients who develop resistance to rifampicin have been treated with good results (90% sputum conversion and 8% relapse) with a regimen based on high doses of isoniazid (900 mg/day with pyridoxine 50 mg), ethambutol (25 mg/kg/day), sulfamethoxazole (1 g thrice daily), and streptomycin or amikacin (for the first 2 or 3 months)

until 12 to 15 months of negative cultures have been obtained.[76,77] The inclusion of clarithromycin in this regimen may obviate the need for the initial 2 or 3 months of aminoglycoside therapy; the role of the new quinolones has yet to be defined.[1,26,84]

In HIV-seropositive patients being treated with antiretroviral agents who present disease caused by *M kansasii*, treatment is complicated because of the way rifamycins (rifampicin more than rifabutin) interact with protease inhibitors and nonnucleoside reverse-transcriptase inhibitors. Treatment recommendations similar to those healing with the treatment of HIV-infected patients with tuberculosis have been published. Some of these guidelines are updated periodically and can be accessed on the Internet. They provide up-to-date information on the changes of drugs or dose adjustments needed depending on the antiretroviral agents being used (Table 4).[85-87]

Surgery is currently not indicated for patients with disease caused by *M kansasii.* Surgical treatment should only be considered in patients with localized and resectable disease who fail to achieve negative sputum cultures because of resistant strains or intolerance to medication.

Treatment of M avium *Complex*

The greatest advance in the treatment of infection caused by *M avium* complex occurred with the introduction in the early 1990s of the new macrolides-azolides (clarithromycin and azithromycin). These antimicrobial agents have excellent in vitro activity, achieve high intracellular concentrations (a factor that may be advantageous as most of the mycobacteria are contained within the phagolysosomes of macrophages), and demonstrate their efficacy in clinical trials both when administered as monotherapy and in the context of multidrug therapies.[88-90] Although both azithromycin and clarithromycin are highly effective, the former has been shown to be somewhat more effective than the latter.[91,92] However, notwithstanding their good activity against *M avium* complex, in view of the need for prolonged treatments and the consequent risk of acquired resistance, the use of these drugs as monotherapy is not recommended.[90-94] Several studies have demonstrated the efficacy of treatment regimens including macrolides. Such regimens achieve negative sputum in some 90% of cases,[94-99] making them clearly superior to the treatment regimens based on antituberculosis agents (rifampicin, isoniazid, ethambutol, and streptomycin) used before the advent of the macrolides. Culture conversion rates range from 50% to 70%, and relapse rates are close to 20%.[1,74,100] In studies comparing different doses of clarithromycin (between 500 and 2000 mg/day), better sputum conversion rates were obtained with higher doses, but high dose regimens were also associated with an increase in the number of adverse events and the need for treatment withdrawal.[90,101,102] Consequently, the regimen deemed to give the best results was 1000 mg/day. Rifabutin is another drug that has demonstrated good activity in vitro against *M avium* complex, superior to that of rifampicin[103,104]; rifampicin, moreover, induces hepatic metabolism of clarithromycin to a greater degree than rifabutin, causing a more accentuated decline of clarithromycin levels in serum.[105] Clarithromycin, on the other hand, inhibits the hepatic elimination of rifabutin, thereby increasing the risk of rifabutin toxicity.[106,107]

Although it has not yet been established which drug combination is the most potent and best tolerated, in light of the data mentioned above the treatment should be a combination of at least 3 drugs[1,4,108]: clarithromycin (500 mg twice daily) or azithromycin (250 mg/day or 500 mg 3 times a week), rifampicin (600 mg/day) or rifabutin (300 mg/day), and ethambutol (25 mg/kg/day for the first 2 months followed by 15 mg/kg/day). In patients with extensive disease, intermittent treatment with an aminoglycoside (streptomycin or amikacin) during alternate weeks for the first 2 or 3 months at a weight- and age-adjusted dose is recommended if kidney function is normal. Kanamycin has also been shown to be effective during in the early stages.[96] Older patients (over 70 years) and patients with low weight are better able to tolerate clarithromycin at a dosage of 250 mg twice a day or azithromycin at a dose of 250 mg 3 times a week.[102] The optimal duration of treatment is not known, but it is considered acceptable to continue treatment until sputum has been negative for 12 months.[1,4,94,95] Clinical improvement occurs after 3 to 6 months, and conversion to culture negative within 6 to 12 months. If there is no response within this period, the possibility of patient nonadherence to treatment or a resistant microorganism should be investigated. In recent years, studies in which the drugs were administered 3 times a week have demonstrated efficacy very similar to that of a daily dose, although results were somewhat better when clarithromycin was used.[97,98,109]

When a treatment regimen containing a macrolide fails because of resistance or intolerance, the following 4-drug regimen recommended by the ATS in 1990[110] can be tried: isoniazid (300 mg/day), rifampicin (600 mg/day), ethambutol (25 mg/kg/day for the first 2 months followed by 15 mg/kg/day) plus streptomycin for the first 3 to 6 months, with a duration of 18 to 24 months and until cultures have been negative for at least 12 months; rifabutin can be used as an alternative to rifampicin.[1] Other drugs that can be used are as follows: clofazimine, ethionamide, amikacin, kanamycin, cycloserine, and the fluoroquinolones that have been shown to be active against *M avium* complex (ofloxacin, ciprofloxacin, levofloxacin, and moxifloxacin).[111] Tests have revealed that moxifloxacin has the greatest activity in vitro,[111-113] but its role in the treatment of *M avium* complex has yet to be determined. In patients who do not tolerate first line antituberculosis agents, the following is an alternative regimen that can be effective: ciprofloxacin (750 mg twice daily) or ofloxacin (400 mg twice daily), clofazimine (100 mg/day), ethionamide (250 mg 2 or 3 times a day), plus streptomycin or amikacin.[1,4]

Pharmacotherapy is currently the treatment of choice for infections caused by *M avium* complex although surgery has achieved some acceptable results in the treatment of these patients, especially before the introduction of the macrolides. Surgery is, however, associated with high morbidity and mortality rates, making it an option to be considered only in patients with localized pulmonary disease in whom pharmacological treatment has failed because of resistant strains or intolerance to the drugs.[114,115]

Since infection with *M avium* complex increases mortality in patients with AIDS,[116,117] treatment and prophylaxis are indicated. In immunocompromised patients the most common clinical presentation is disseminated disease, although the use of more effective antiretroviral therapies and the administration of prophylaxis against *M avium* complex has considerably reduced the incidence of new cases.[118] The treatment regimens are the same as those described above for immunocompetent patients, but the prescribing physician must take into account the increase in the adverse events caused by medication and the possible interactions between the antimicrobial and the antiretroviral agents (protease inhibitors and nonnucleoside reverse transcriptase inhibitors), making the opportune changes in the drug and dosage regimens used depending on the antiretroviral agent or combination of such agents the patient is taking. Guidelines on this topic have been published; some are continuously updated and can be accessed online (Table 4).[86-88] The multidrug combination of clarithromycin or azithromycin, ethambutol, and rifabutin (which is subject to fewer interactions than rifampicin) is the preferred regimen[1,4]; the addition of an aminoglycoside (streptomycin or amikacin) in the initial stages in patients with severe symptoms can be considered.[1] This regimen was shown to be more effective than the combination of rifampicin, ethambutol, clofazimine, and ciprofloxacin.[100] The addition of clofazimine to the combination of clarithromycin and ethambutol is not recommended because it has been reported that this combination increases mortality (from 38% to 61%).[119] The role of other drugs, such as the quinolones, ethionamide, cycloserine, and telithromycin has not yet been determined. The optimum duration of treatment is unknown, and patients who remain immunodeficient may require prolonged treatment. With the introduction of more effective antiretroviral therapies, many patients achieve reconstitution of the immune system, and recent studies have demonstrated potential cure of disease caused by *M avium* complex and the possibility of safely discontinuing treatment.[120-122] Nonetheless, follow up is recommended to confirm that the viral load has been suppressed and that the CD4+ lymphocyte count is maintained. The length of time that should be allowed to elapse after reconstitution of the immune system before treatment is discontinued has not been determined; however a minimum treatment period of 12 months and 6 months after reconstitution of the immune system is considered adequate.[123,124]

Prophylaxis Against M avium *Complex Infection in HIV-Positive Patients*

Patients with HIV infection present a high risk of disseminated infection caused by *M avium* complex if their CD4+ lymphocyte count falls below 50 cells/μL, and such patients should receive chemoprophylaxis.[1,123,124] Randomized controlled trials have demonstrated the efficacy of rifabutin 300 mg/day,[125] clarithromycin 500 mg twice daily,[126,127] and azithromycin 1200 mg once a week[128,129] as prophylaxis against disseminated disease caused by *M avium* complex. Two recent trials showed that clarithromycin and azithromycin are more effective than rifabutin[127,128] and have fewer interactions, making them the preferred drugs for primary prophylaxis against *M avium* complex.[62,124] One drawback is the possible development of resistance (something that does not generally happen with rifabutin).[93] Since the combination of clarithromycin and rifabutin is no more effective than clarithromycin alone as chemoprophylaxis, and given that it is associated with more adverse events, this combination should not be used.[127] The combination of azithromycin with rifabutin has been shown to be more effective than azithromycin alone, but in light of the increase in adverse events, possible interactions, and the higher cost, the use of this combination is not recommended.[128] If clarithromycin or azithromycin is not tolerated, rifabutin is the recommended alternative drug, and in such cases the possibility of tuberculosis infection should be ruled out in order to avoid monotherapy.[124,129] In patients who respond to antiretroviral treatment and whose CD4+ lymphocyte count remains above 100 cells/μL for 3 months, primary prophylaxis against *M avium* complex should be discontinued[124,129] because it has been shown that the risk of developing *M avium* complex infection is minimal in such cases.[130-133] Prophylactic therapy should be restarted if the CD4+ lymphocyte count falls below 50 to 100 cells/μL.[124]

Treatment of Infection Caused by Other Slow Growing EM

Many species that can produce pulmonary disease have been described. Since most of the case series deal with small numbers of patients and a sufficient number of treatment trials have not been undertaken, it is impossible on the basis of the available data to define treatment recommendations with any scientific rigor. Treatment should been maintained for 18 to 24 months after a satisfactory clinical and bacteriological response has been obtained.[1]

In a recent BTS study,[50,74] in vitro susceptibility tests of *M xenopi* indicated high levels of resistance, but this was not associated with treatment failure or relapse rates, which were similar in both patients infected with resistant strains and those infected with susceptible strains. This phenomenon has been mentioned in a previous review.[134] In the BTS trial, rifampicin and ethambutol were compared with rifampicin, ethambutol,

plus isoniazid. Both combinations were administered for 2 years. The response/relapse rate was slightly better with the latter combination, but the difference was not statistically significant. A BTS trial currently underway is comparing the combination of rifampicin, ethambutol, and ciprofloxacin with rifampicin, ethambutol, and clarithromycin. That study may shed light on the roles of the quinolones and macrolides. The ATS recommends treatment with a macrolide, rifampicin or rifabutin, and ethambutol, with or without streptomycin in the initial stages, for 18 to 24 months with at least 12 months of negative cultures.[1] If treatment fails or the patients relapses, surgery may be considered.[134,135]

M malmoense. As in the case of *M xenopi,* the response of *M malmoense* to treatment is unrelated to the presence of resistance revealed by in vitro testing.[55,56,74,136] In a BTS[55] study of 106 patients, no differences were found between rifampicin, ethambutol, and isoniazid, and rifampicin plus ethambutol when both combinations were administered for 2 years. Since it is better tolerated and achieves rates of response similar to the previously recommended regimens comprising 4 or 5 drugs, the latter combination is the regimen currently recommended by the BTS (pending the results of the trials studying the addition of a macrolide or a quinolone).[57,136]

Mycobacterium simiae. Most *M simiae* isolates are resistant to first line antituberculosis agents. The recommended initial treatment is a combination of 4 drugs (clarithromycin, ethambutol, rifabutin, and streptomycin), which should be modified according to the results of susceptibility tests.[1,4]

M szulgai. M szulgai, which is considered to be a pathogen when isolated in humans, can cause disease in the lungs, other sites, and disseminated disease.[137] It is susceptible to rifampicin and to high concentrations of isoniazid, streptomycin, and ethambutol. Treatment with these 4 drugs is recommended.[1]

M terrae. M terrae is susceptible in vitro to the macrolides (clarithromycin and azithromycin) and, less frequently, to ethambutol and rifampicin. Treatment with clarithromycin, ethambutol, and rifampicin is recommended.[47,48]

M asiaticum. No treatment regimen has been established. Good results have been obtained with regimens that combine rifampicin and ethambutol plus an aminoglycoside and isoniazid or pyrazinamide.[138,139]

Mycobacterium genavense. The treatment regimen for *M avium* complex is also recommended for cases of infection with *M genavense*.[140,141]

Treatment of Infection with Rapidly Growing EM

Rapidly growing mycobacteria are characterized by their resistance to the first line antituberculosis drugs and by their susceptibility to various common antibiotics. Given the variability between species and groups, susceptibility tests should always be carried out in order to determine the most effective treatment, and the drugs tested should include conventional antimicrobial agents. *M fortuitum* is susceptible to a number of oral antibiotics including the fluoroquinolones, the newer macrolides, sulfonamides, and, to a lesser degree, doxycycline and minocycline. It is also susceptible to parenteral agents, including amikacin, imipenem, and cefoxitin. *M abscessus* is susceptible to clarithromycin, amikacin, cefoxitin, and, less often, to imipenem. *M chelonae* is susceptible to clarithromycin, amikacin, tobramycin (more often than to amikacin), less frequently to imipenem, and in some cases to the quinolones and doxycycline.[142,143] Lung disease caused by these mycobacteria requires long periods of treatment (6 to 12 months). *M fortuitum* is the rapidly growing EM that has the best response because it is susceptible to oral drugs; treatment with a combination of 2 oral agents to which it is susceptible is recommended. Treatment of *M abscessus* and *M chelonae* is more complicated and yields poorer results because the parenteral drugs that must be used are less well tolerated; a combination of clarithromycin with 1 or 2 parenteral drugs (amikacin, cefoxitin, or imipenem) is the recommended regimen. However, in many cases, surgical resection is needed to achieve a cure when the lung involvement is localized.[1,43,44,144] New drugs, such as the ketolides (telithromycin), oxazolidinones (linezolid), and glycylcyclines (tigecycline/GAR-936), have been shown to have good in vitro activity against rapidly growing EM; these new agents could therefore play a role in treatment.[144-148]

In summary, there has been an increase in recent years in infections caused by EM, and treatment is a challenge for doctors because of the complexities involved in the management of many of these patients. However, their prognosis has improved considerably with the emergence of new antimicrobial agents that are more active against EM and of new antiretroviral agents that are more potent against HIV.

Patients should be monitored closely during regular checkups to assess the clinical course of the disease, the occurrence of adverse events, and any possible drug interactions. Bacteriologic studies should also be performed periodically as should the appropriate blood tests and radiographic assessments. For all of these reasons, it is recommended that these patients be treated by expert personnel in specialized hospitals and clinics.

Conclusions

The isolation of EM is increasingly more common because of improvements in culture media and identification techniques. These improvements have also led to the discovery of new species. The clinical importance of EM as a cause of disease has also increased, particularly with the onset of the AIDS epidemic, although antiretroviral treatments, given their

efficacy, have produced a decline in the number of cases of disease due to EM and particularly in the incidence of disseminated forms of the disease. EM diseases generally affect immunodepressed patients and patients with a history of lung disease, but a considerable proportion of cases involve previously healthy patients. While the clinical presentation of the pulmonary disease caused by these mycobacteria varies, it usually includes the signs and symptoms characteristic of tuberculosis. However, certain forms of the disease are more difficult to diagnose, especially presentations that take the form of bronchiectasis and nodules. In these cases, suitable diagnostic techniques should be used (the CT scan is a valuable imaging technique). To establish a firm diagnosis and start treatment, the physician must take into account the following data: the clinical picture (symptoms, predisposing factors, and the state of the patient's immune system), radiographic images, and microbiological results (number, intensity, type of sample). Clinical monitoring is an option if there is any doubt about whether the patient is in fact affected by EM disease. In patients with disease, treatment according to published recommendations should be started. However, whether to begin treatment and the optimum duration of same should always be decided on a case-by-case basis in light of the causative pathogen, the clinical characteristics of the case, and the patient's response to treatment.

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